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Re: European Patent EP 0 139 417
Opposition by Chiron Corporation
Genentech Docket: 100/152,233

EXHIBIT G

I, John K. Rose, Ph.D., do declare as follows:

1. On December 14, 1990, I executed a Declaration in support of a reply by Genentech, Inc. (Genentech) to an opposition by Chiron Corporation (Chiron) in connection with Genentech's European Patent No. 0 139 417. A complete copy of my Declaration is attached. I hereby reaffirm all of the statements made in the attached Declaration.

2. I understand that Chiron has now alleged that the opinions stated in my Declaration are not entirely my own. I strongly disagree with these allegations.

3. In the fall of 1990, I was approached by an attorney, Daniel E. Altman, who informed me that he was working on behalf of Genentech in connection with the opposition referred to above. Mr. Altman further informed me that this opposition concerned the work of Genentech researchers, Laurence Lasky and Phillip Berman, regarding their recombinant herpesvirus vaccine. This work related to my primary research interest of the intracellular transport of viral membrane proteins. Accordingly, I was already generally familiar with the work of Drs. Lasky and Berman.

4. Due to my familiarity with these researchers' work, I agreed to review Genentech's patent application, as well as the prior art cited by Chiron in their opposition. After completing this review, I discussed my opinion concerning the nature and predictability of the invention with Mr. Altman. This opinion was based on my review of these documents and on my knowledge of the state of the art at the time this application was filed.

5. Based on our discussion, Mr. Altman prepared a draft Declaration that set forth my qualifications and summarized my opinions. I reviewed this draft and requested that several changes be made. Mr. Altman made the changes and again submitted the draft for my review. I requested that further clarifications be made to the revised draft before finally agreeing that the Declaration accurately set forth my opinions.

6. I understand that Chiron has questioned the statement I made in paragraph 8 of my earlier Declaration concerning the ability of one of ordinary skill in the art to have predicted in August 1983 whether a successful vaccine could have been produced using the process claimed by Genentech. My statement was based on my knowledge of the state of the art at that time. As of August 1983, there had been no previous reports of a vaccine that conferred *in vivo* protection against a pathogen based solely on a truncated, membrane-free

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derivative of a viral glycoprotein. (See paragraph 7 of my earlier declaration.) Accordingly, it was not yet known whether such a glycoprotein could give rise to the immune response necessary to confer *in vivo* protection. Moreover, as explained below, it could not have been predicted in August 1983 that such protection would have been conferred.

7. The Gething et al., *Nature*, 300:598-603 (1982) reference cited by Chiron relates to the production of a truncated, membrane-free derivative of haemagglutinin of influenza virus. I was well aware at the time of my earlier declaration that this reference contains an unsubstantiated statement in its penultimate paragraph that the work reported therein could lead to a method for vaccine production. The reference does not contain any other discussion of vaccines. Notwithstanding anything in this Gething et al. reference, one of ordinary skill in the art could not have predicted that a successful vaccine could be produced based on its teachings.

8. As was well known in August 1983, there are a number of significant technical obstacles that must be overcome in order to produce from an isolated glycoprotein a successful vaccine that provides immunoprotection against a pathogen. First, it must be shown that the particular glycoprotein selected actually raises neutralizing antibodies against the pathogen. No such showing is present in the Gething et al. paper. Moreover, it was also well known in August 1983, that *in vivo* protection against a pathogen can often require more than the mere ability to raise antibodies that are neutralizing *in vitro*.

9. Many instances are known in which large numbers of neutralizing antibodies are raised, yet fail to protect the host from pathogenesis. In many instances, pathogens are capable of altering their immunogenic profile so as to escape inactivation by antibodies raised solely against a single glycoprotein. Examples of such pathogens include Equine Infectious Anemia Virus (EIAV), Visna Virus, trypanosomes and HIV-1 (known in 1983 as HTLV-III).

10. Further, as of 1983, it was not known whether a T cell response was required in order to provide protection against many viral pathogens. It was widely thought in 1983 that such cellular immunity was essential to provide an effective vaccine against a viral pathogen, and it was not known if a truncated glycoprotein could evoke such a response.

11. Moreover, those having ordinary skill in the art would not have known whether polyvalent complexes were necessary to provide immunogenicity. For the influenza virus haemagglutinin, Mary Jane Gething, the lead author of the Gething et al. reference, was quoted in Zoller et al., *Bio/Technology*, pp.146-147 (April 1983), as stating that "[c]learly, one needs polyvalent complexes [of HA molecules] for immunogenicity." However, unexpectedly, Lasky and Berman demonstrated that a single truncated, membrane-free derivative of herpes simplex virus (HSV) gC or gD glycoprotein could successfully protect animals from infection by HSV.

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12. Thus, as of the effective filing date of this application, it could by no means be predicted that a successful vaccine could be produced based solely on a single truncated, membrane free derivative of a viral glycoprotein. One of ordinary skill in the art at the relevant date could not have predicted whether such a glycoprotein would elicit neutralizing antibodies that would be effective in preventing pathogenesis, whether the antibodies alone without a cellular immune component could be effective, nor whether a complex of glycoproteins was required for immunogenicity. Thus, in August 1983, one of ordinary skill in the art would not have had sufficient information to predict Lasky's and Berman's successful results.

13. In paragraph 9 of my earlier declaration, I stated that once Drs. Lasky and Berman demonstrated the successful production of a vaccine in their HSV model that a reasonable expectation arose that the system would be successful with other viral pathogens. This expectation arose because the successful results produced in the HSV model demonstrated that all of the technical challenges to successful vaccine production had been overcome. In other words, Lasky's and Berman's successful production of a vaccine effective against a viral pathogen based on a truncated, membrane-free viral glycoprotein showed that such a glycoprotein could elicit neutralizing antibodies and that such antibodies could be raised against a single glycoprotein. Lasky's and Berman's successful work further showed that such antibodies could be effective in preventing pathogenesis, and that any necessary cellular immune component must have been generated. The work of Gething et al. showed nothing with respect to these technical obstacles. Thus, the Gething et al. work did not give rise to any expectation of success.

14. I understand that I was quoted in the Zoler et al. article referred to above, as stating that the idea that removal of the anchor sequence could convert these proteins from a membrane-bound to a secretory form was "pretty much obvious to everybody." This is certainly what was expected at the time the Gething et al. reference referred to above was published. However, as explained above, the expectation that the proteins could be secreted suggests nothing regarding whether the secreted proteins would provide an effective vaccine.

15. I declare that all statements made herein of my own knowledge are true, and that all statements made upon information and belief are believed to be true, and, further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, and that willful, false statements may jeopardize the validity of the patent.

Dated: Dec. 20, 1993

By: John K. Rose
John K. Rose, Ph.D.

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